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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,007	04/26/2001	Jens Kossmann	GFB-1 DIV1	9893
1473	7590	11/14/2003	EXAMINER	
FISH & NEAVE 1251 AVENUE OF THE AMERICAS 50TH FLOOR NEW YORK, NY 10020-1105			BAUM, STUART F	
			ART UNIT	PAPER NUMBER
			1638	

DATE MAILED: 11/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/843,007	Applicant(s) KOSSMANN ET AL.	
	Examiner Stuart F. Baum	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2003 and 18 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,8 and 19-47 is/are pending in the application.
- 4a) Of the above claim(s) 2,8,19,22-32,39 and 42-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20,21,33-38,40,41 and 47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 08/737,752.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The amendments filed on 3/24/2003 and 8/18/2003 have been entered.

Claims 2, 8, 19-47 are pending.

Claim 47 has been newly added.

Claims 2, 8, 19, 22-32, 39, 42-46 are withdrawn from consideration because they are drawn to non-elected subject matter.
2. Claims 20-21, 33-38, 40-41, and 47 are examined in the present office action.
3. This application contains claims 2, 8, 19, 22-32, 39, 42-46 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancelation of nonelected claims (37 CFR 1.144) See MPEP § 821.01.
4. Rejections and objections not set forth below are withdrawn.
5. The text of those sections of Title 35, U.S. Code not included in this office action can be found in a prior office action.

Indefiniteness

6. Claims 20-21, 33-38, 40-41, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection includes dependent claims.

In claim 1, it is recommended that the word "homologous" be replaced with --sequence identity--. The meaning of the word "homologous" is indefinite as it is not clear how relatedness

is determined, whether by sequence relatedness alone, by evolutionary relatedness, or by some other means. All subsequent recitations of "homologous" are also rejected.

In claims 1, 6th line, replace "having" with --comprising--, to better clarify Applicants' invention.

In claim 1, (d) and (e), it is unclear if the deposit number DSM 9196, corresponds with the plasmid pNB2 or the Neisseria bacteria. Correction is required. All subsequent recitations of deposit number DSM 9196 are also rejected.

Written Description

7. Claims 20-21, 33-38, 40-41, and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method or process for the production of linear α -1,4 glucans, fructose and/or fructose syrup comprising culturing a host cell or microorganism comprising a first DNA sequence encoding an amylosucrase wherein the DNA sequence exhibits more than 60% sequence identity to the following: a DNA sequence coding for a protein having SEQ ID NO:2, or the coding region of SEQ ID NO:1, or a DNA sequence encoding a protein having amylosucrase activity wherein the DNA sequence is from the insert of plasmid pNB2 from Neisseria bacteria having deposit number DSM 9196, or a DNA sequence encoding a protein wherein the DNA sequence is from the insert of plasmid pNB2 from Neisseria bacteria having deposit number DSM 9196, or a part of any of the above sequences coding for a protein having

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the enzymatic activity of an amylosucrase, or a full length complement of any of the above sequences; wherein the host cell or microorganism secretes amylosucrase into a culture medium comprising sucrose and recovering the produced α -1,4 glucans and/or fructose, or wherein any one of the above sequences are transformed into a plant and the encoded protein is targeted to a vacuole or to the apoplast.

The Applicants disclose the isolation of a genomic sequence encoding an amylosucrase from *Neisseria polysaccharea* which was subcloned into the vector pNB2 and transformed into *E. coli*. Amylosucrase was detected both within *E. coli* and in the medium in which the *E. coli* were grown. The Applicants do not identify structural features unique to the *N. polysaccharea* amylosucrase protein, the functional domains of the protein nor the overall function of the protein. The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Given the lack of description for the *N. polysaccharea* amylosucrase protein, it remains unclear what features identify a *N. polysaccharea* amylosucrase protein or a DNA sequence exhibiting more than 60% sequence identity to the following: a DNA sequence coding for a protein having SEQ ID NO:2, or the coding region of SEQ ID NO:1, or a DNA sequence encoding a protein having amylosucrase activity wherein the DNA sequence is from the insert of plasmid pNB2 from *Neisseria* bacteria having deposit number DSM 9196, or a

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DNA sequence encoding a protein wherein the DNA sequence is from the insert of plasmid pNB2 from *Neisseria* bacteria having deposit number DSM 9196, or a part of any of the above sequences coding for a protein having the enzymatic activity of an amylosucrase, or a full length complement of any of the above sequences. Since a *N. polysaccharea* amylosucrase protein has not been described by specific structural features or by specific function, the specification fails to provide an adequate written description to support the generic claims.

Response to Applicants' Arguments

Applicants contend that they have described the claimed sequences by stating in the claims that the nucleic acid sequences have at least 60% sequence identity to SEQ ID NO:1 or nucleic acids encoding SEQ ID NO:2 (page 12, 1st full paragraph). Applicants also recite a function for the claimed sequences in that the sequences have to have amylosucrase activity. Applicants also provide an assay to readily determine amylosucrase activity. Applicants point to places in the specification where an assay for detecting amylosucrase activity can be found (page 13, top paragraph).

The Office contends that Applicants have not defined the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the genus does, rather than what it is. Applicants have not disclosed the domains that are conserved or important for the proper functioning of the protein. Specifying sequences with at least 60% sequence identity to nucleic acids that encode SEQ ID NO:2 does not specify which amino acids are important and which amino acids can be added, deleted, or substituted without changing the activity of the polypeptide of SEQ ID NO:2.

Enablement

8. Claims 20-21, 33-38, 40-41, and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing linear α -1,4 glucans comprising a nucleic acid sequence encoding an amylosucrase from *Neisseria polysaccharea*, which includes the plasmid pNB2, transformed into bacteria to yield amylosucrase, wherein the amylosucrase is incubated with sucrose under conditions that allow said protein to produce linear α -1,4 glucans does not reasonably provide enablement for a method or process for the production of linear α -1,4 glucans, fructose and/or fructose syrup comprising culturing a host cell or microorganism comprising a first DNA sequence encoding an amylosucrase wherein the DNA sequence exhibits more than 60% sequence identity to the following: a DNA sequence coding for a protein having SEQ ID NO:2, or the coding region of SEQ ID NO:1, or a DNA sequence encoding a protein having amylosucrase activity wherein the DNA sequence is from the insert of plasmid pNB2 from *Neisseria* bacteria having deposit number DSM 9196, or a DNA sequence encoding a protein wherein the DNA sequence is from the insert of plasmid pNB2 from *Neisseria* bacteria having deposit number DSM 9196, or a part of any of the above sequences coding for a protein having the enzymatic activity of an amylosucrase, or a full length complement of any of the above sequences; wherein the host cell or microorganism secretes amylosucrase into a culture medium comprising sucrose and recovering the produced α -1,4 glucans and/or fructose, or wherein any one of the above sequences are transformed into a plant and the encoded protein is targeted to a vacuole or to the apoplast. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The Applicants do not reduce to practice the full scope of their invention. They only disclose the isolation of a genomic sequence encoding an amylosucrase from *Neisseria polysaccharea* which was subcloned into the vector pNB2 and transformed into *E. coli*. Amylosucrase was detected both within *E. coli* and in the medium in which the *E. coli* were grown. Both soluble and insoluble products were detected in the growth medium and the soluble products are short-chained polysaccharides. The chain length was between approx. 5 and approx. 60 glucose units (page 36, top paragraph). But, Applicants go on to state that it was not possible to detect branching in the synthesis products (last sentence of top paragraph). The Applicants have not demonstrated that α -1,4 glucans, fructose and/or fructose syrup can be produced and isolated from: a plant transformed with an amylosucrase.

Producing α -1,4 glucans using amylosucrase does not always produce the expected results. Applicant's own admitted statement that products, other than the desired α -1,4 glucans

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were produced even in their system (page 36, lines 3-12). Remaud-Simeon et al (1995, Carbohydrate bioengineering. Proceedings of an International Conference, Elsinore, Denmark. Pages 313-320. Vol 10 in the series, Progress in Biotechnology) teach that concentrations of sucrose higher than 30 g/l inhibit the amylosucrase and the enzyme is not only activated by sucrose but also by glycogen, starch and maltooligosaccharides (page 319, 2nd paragraph). Remaud-Simeon et al conclude that the enzyme is activated by glycogen, starch and maltooligosaccharides and can catalyze other reactions (abstract). de Montalk et al (2000, FEMS Microbiology Letters 186(1)103-108) teach that glycogen is an activator of amylosucrase and that this interaction is sucrose concentration dependent (page 106, 1st paragraph of Discussion). De Montalk points out that sucrose and glycogen both bind to the enzyme (page 106, 1st paragraph of Discussion and page 107, 3rd paragraph), and that the enzyme has binding sites for other carbohydrates, not just sucrose (abstract). de Montalk et al (2000, FEBS Letters 471 (2/3):219-223) teach that amylosucrase synthesizes a large diversity of products in the presence of sucrose as a sole substrate and that the enzyme is capable of several different reactions in a non-Michaelian kinetic behaviour (page 223, Conclusion paragraph). Albenne et al (2002, FEBS Letters 527(1-3):67-70) teach that amylosucrase from *Neisseria polysaccharea* can catalyze reactions other than the cleavage of the alpha 1-beta 2 linkage of sucrose (page 70, 1st paragraph).

It cannot be predicted by one of skill in the art that Applicants' claimed sequences will encode a protein with the same activity as SEQ ID NO:2. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures

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that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column). The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by McConnell et al (2001, Nature 411 (6838):709-713), who teach that the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain. This change renders the protein constitutively active and therefore creates a dominant mutation which has a drastic alteration in phenotype compared to wild-type *Arabidopsis* plants.

It would cause undue experimentation by one skilled in the art to identify and isolate a sequence exhibiting more than 60% sequence identity to either a nucleic acid encoding SEQ ID NO:2, or the coding region of SEQ ID NO:1, or the DNA insert of plasmid pNB2, or a part of any of the previously mentioned sequences. Each putative sequence would have to be individually subcloned into an expression construct and then transformed into bacteria capable of expression said subcloned sequence. The encoded protein would have to be isolated and

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tested for proper activity. Given the breadth of the claims, a multitude of sequences would have to be tested to find one that produces the expected results.

Given the claim breadth, unpredictability and lack of guidance as stated above; given the breadth of the claims which encompass a multitude of sequences that have not been exemplified; it would require undue experimentation by one skilled in the art to identify and isolate a multitude of non-exemplified nucleic acid sequences encoding a protein having the activity of an amylosucrase from a multitude of non-exemplified plants or other organisms, and to evaluate the ability of these sequences or variants thereof to have the expected activity.

Response to Applicants' Arguments

Applicants contend that they are not required to produce an Example in which they disclose a plant transformed with an amylosucrase that produced α -1,4 glucans. Applicants contend that they disclose methods of making transgenic plants in the specification and that one of ordinary skill in the art could make and use Applicants' claimed invention.

The Office contends that given the unpredictability as stated above; given the breadth of the claims which include unexemplified sequences, and given a lack of working examples or disclosure which explicitly directs the skilled artisan, undue experimentation would be required to make and or use the claimed invention.

Applicants contend that Remaud-Simeon et al reference does not teach unpredictability, but rather, that α -1,4 glucans can be made without the need of an activator, and that significant amounts of α -1,4 glucans can be made when no activator is present. Applicants also contend that deMontalk et al actually supports Applicants' claim that amylosucrase produces α -1,4 glucans from sucrose or that α -1,4 glucans are the major product formed by contacting an amylosucrase

with sucrose. Applicants contend that de Montalk et al (FEMS Microbiol. Letts. 186:103-108, 2000) teach that there is not an additional binding site for substrates other than sucrose, but rather that amylosucrase has two separate binding sites for sucrose. Applicants contend that de Montalk has not confirmed that the second binding site is utilized by other carbohydrates (page 17, middle paragraph). Applicants contend that de Montalk et al (FEBS Letts., 471 :219-223) support Applicants' claims that amylosucrase produces linear α -1,4 glucans and that under all conditions tested, the majority of products made by amylosucrase were α -1,4 glucans. Applicants contend that Albenne et al teaches that amylosucrase in the presence of linear α -1,4 glucans, not sucrose, results in the formation of linear maltooligosaccharides-still a linear α -1,4 glucans.

The Office contends that the above references do teach a level of unpredictability when using amylosucrase to produce α -1,4 glucans, even though they may also support Applicants' demonstration that a nucleic acid molecule isolated from *Neisseria* bacteria encodes an amylosucrase that can be used to produce α -1,4 glucans. But, given Applicants' broad claims, the state-of-the-art as recited above, does teach unpredictability in producing linear α -1,4 glucans. Applicants have not taught making linear α -1,4 glucans in plants. See *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Deposit Rejection

9. Claims 20-21, 33-38, 40-41, and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Since the plasmid or microbe claimed is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If a plasmid or microbe is not so obtainable or available, the requirements of 35 U.S.C. 112 may be satisfied by a deposit thereof. The specification does not disclose a repeatable process to obtain the exact same plasmid or microbe in each occurrence and it is not apparent if such a plasmid or microbe is readily available to the public. It is noted that applicants have deposited plasmid or microbe under the depository numbers: DSM 9196, but there is no indication in the specification as to public availability. If the deposit of these plasmid or microbe is made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the plasmid or microbe will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit, meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) the viability of the biological material at the time of deposit will be tested (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

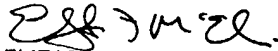
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 703-305-6997. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Stuart F. Baum Ph.D.

November 5, 2003


ELIZABETH F. McELWAIN
PRIMARY EXAMINER
GROUP 1600